IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Shaker A. Mousa

Group Art Unit: 1623

Application No.: 10/667,216

Examiner: Lau, Jonathan S.

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Docket No.: **MOUSA-4618**

Title: **OXIDIZED HEPARIN FRACTIONS AND THEIR USE IN INHIBITING ANGIOGENESIS**

Commissioner for Patents
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REPLY BRIEF OF APPELLANT

This Reply Brief is in response to the Examiner's Answer mailed October 27, 2009.

The arguments by the Examiner for rejecting the claims are the same in the Examiner's Answer as in the Final Office Action mailed October 27, 2008. Therefore, Appellant's arguments in the Appeal Brief, which traverse the Examiner's arguments for rejecting the claims, will not be repeated here.

This Reply Brief specifically addresses the discussion appearing in "Response to Argument" beginning on page 14 of the Examiner's Answer.

GROUND OF REJECTION 2

Claims 1, 2, 5, 6, 43 and 91-94 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892).

The Examiner's Answer, in "Response to Argument", responds to Appellant's arguments in the Appeal Brief with respect to the rejections of claims 1, 2, 5, 6, 43, 91-94 under 35 U.S.C. 102(b) as allegedly being anticipated by Naggi.

Claim 1

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 1:

"wherein the super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis"; and

"wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction".

The Examiner's Answer, in "Response to Argument", argues:

"Appellant contends that Naggi does not teach or disclose each and every feature of claim 1. Appellant again cites Lundin, Journal of Biological Chemistry, vol. 275, no. 32, (August 11, 2000) as providing evidence that it is known in the art that desulfation results in inhibition of FGF-2 induced angiogenesis. However, Naggi discloses that the invention of Naggi is drawn to a

depolymerized heparin that possesses a sulfation degree at least 20% higher than that of starting heparin (column 5, lines 5-10). As noted by Appellant, Naggi does not teach or provide evidence that the compound disclosed by Naggi possess the characteristic of inhibiting of FGF-2 induced angiogenesis. However, this is deemed to be **an inherent property** of the chemical disclosed by Naggi, meeting the structural limitations of the instant invention as claimed." (emphasis added)

In response, Appellant asserts that under case law, the alleged inherency (that the claimed chemical structure in claim 1 is inherently disclosed by Naggi) must **necessarily and inevitably** follow from the teachings in the prior art (i.e., from Naggi) and a high probability of occurrence is not sufficient demonstrating inherency. See MPEP 2112(IV) which recites: "**The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.** *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)... "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows

from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)" (bold emphasis added).

Appellant next argues that the Examiner's allegation that the claimed chemical structure in claim 1 is inherently disclosed by Naggi is incorrect, because the claimed chemical structure in claim 1 does not ***necessarily*** flow from the teachings of Naggi, but rather is subject to ***uncertainty***.

With respect to the alleged inherency, the Examiner's Answer, in "Response to Argument", argues: "As recited in the body of the rejection above, the compound disclosed by Naggi meets the structural limitations of the invention as claimed. Appellant asserts that the structure disclosed by Naggi does not meet the structural limitations of the invention as claimed by reemphasizing the language of the claim, however these limitations are met by the structure disclosed by Naggi even though Naggi does not use the exact language found in the instant claim. The product-by-process is described by the process of having been "O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction", and said process would make the structure disclosed by Naggi. It is noted that the instant specification discloses oxidation of heparin fractions using **any** oxidizing agent **without limitation,** including reagents such as peroxide and 0_2 (instant specification, page 8, paragraph 26)."

In response, Appellant traverses the preceding allegation that the limitation of "wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at

oxygen bonds within repeating units of the first oxidized heparin fraction" is a product-by-process limitation. Appellant asserts the preceding limitation does not recite how the super-sulfated oxidized heparin fraction of claim 1 is actually produced. Rather, the preceding limitation recites "wherein the super-sulfated oxidized heparin fraction has a chemical structure of ..." for the purpose of describing the chemical structure of the claimed super-sulfated oxidized heparin fraction. In other words, the preceding limitation recites a limitation on the chemical structure of the claimed super-sulfated oxidized heparin fraction irrespective of how the sulfate substitution is implemented.

In further response, Appellant respectfully traverses the preceding allegation in the Examiner's Answer that "the instant specification discloses oxidation of heparin fractions using **any** oxidizing agent **without limitation,** including reagents such as peroxide and 0_2 (instant specification, page 8, paragraph 26)".

Specifically, Appellant cites Par. [0026] of the specification (relied upon in the preceding argument in the Examiner's Answer) which recites: "Oxidation of heparin fractions in accordance with the present invention can be achieved using oxidizing agents, ***including, but not limited to***, periodic acid, metals in high valence states, halogens, halogen atoms, and compounds with O-O bonds, such as O_3, diacyl peroxides, H_2O_2, and O_2. Such oxidizing agents and conditions for oxidation are known in the art and will not be described in detail herein. In one embodiment, oxidation is achieved using a periodate procedure, whereby fractions derived from UFH or super-sulfated heparin, as described below, are oxidized by periodic acid (Fransson, *Carbohydrate Res.*, 62:235-244 (1978); Conrad et al., *Heparin and Related Polysaccharides, Advances in Experimental Medicine and Biology 313*, Lane et al., eds., Plenum Publishing, New

York, pp. 31-36 (1991), which are hereby incorporated by reference in their entirety). Alternatively, UFH or super-sulfated heparin can be oxidized prior to producing heparin fractions as described above. In yet another embodiment, UFH or super-sulfated heparin can be subjected to size exclusion chromatography both before and after oxidation." (emphasis added)

Appellant assert that the phrase "including, but not limited to" in Par. [0026] of the specification is not equivalent to "without limitation" as argued by the Examiner, but rather communications that the oxidizing agents of heparin fractions according to the present invention are not limited to the closed-ended list of "periodic acid, metals in high valence states, halogens, halogen atoms, and compounds with O-O bonds, such as O_3, diacyl peroxides, H_2O_2, and O_2."

In addition, the oxidizing agents that could be used to form the super-sulfated oxidized heparin fraction of claim 1 is even further limited by the recited limitation of "wherein the super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis".

Therefore, contrary to the Examiner's allegation, the specification of the present patent application does not state or imply that **any oxidizing agent without limitation** could be used to form the claimed super-sulfated oxidized heparin fraction that fully inhibits fibroblast growth factor (FGF2) induced angiogenesis.

In addition with respect to the alleged inherency, the Examiner's Answer, in "Response to Argument", further argues: "Naggi uses chlorosulfonic acid, a strong oxidizing agent, to depolymerize the heparin and teaches the prior art uses peroxides to depolymerize heparin (column 4, lines 45-55). While the specification suggests the oxidation converts hydroxyl

residues to aldehydes and acids and provides embodiments wherein a defined percent of the hydroxyl residues are oxidized (instant specification, page 8, paragraph 26), **no structural limitation regarding percent of the hydroxyl residues oxidized is recited in the invention as claimed.** 3Therefore the invention as recited in the instant claims encompasses the compound disclosed by Naggi wherein the heparin is oxidized to depolymerize the heparin".

In response, Appellant cites Par. [0026] of the specification (relied upon in the preceding argument in the Examiner's Answer) which recites: "By oxidation of heparin fractions in accordance with the present invention, hydroxyl residues in the uronic acid and glucosamine monosaccharides are converted to aldehydes, which are then converted to acids. The percentage of hydroxyl residues that are oxidized in accordance with the present invention is determined by the length of incubation with the oxidizing agent and/or the quantity of oxidizing agent used. In one embodiment, from about 25% to about 100% of hydroxyl residues are oxidized. In another embodiment, from about 50% to about 100% of hydroxyl residues are oxidized. In yet another embodiment, from about 90% to about 100% of hydroxyl residues are oxidized."

In further response, Appellant asserts that it does not ***necessarily*** flow from Naggi's alleged teaching that heparin is oxidized to depolymerize the heparin, in combination with the preceding discussion in Appellant's specification, Par. [0026] pertaining to hydroxyl residues, that Naggi's oxidized, depolymerized heparin is the claimed super-sulfated oxidized heparin fraction that fully inhibits fibroblast growth factor (FGF2) induced angiogenesis.

In addition with respect to the alleged inherency, the Examiner's Answer, in "Response to Argument", additionally argues: "The instant specification does not disclose different

structural features responsible for claimed properties such as said first anticoagulant reduction characteristic and said second anticoagulant reduction characteristic, or for fully inhibiting fibroblast growth factor (FGF2) induced angiogenesis. As recited above the compound disclosed by Naggi meets the structural limitations of the invention as claimed and exhibits said second anticoagulant reduction characteristic, therefore there is ***a reasonable expectation*** based on what is disclosed that other characteristics of said compound are necessarily present, see MPEP 2112.01 II, "A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Appellant discloses and/or claims are necessarily present. In re *Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir.1990)"." (emphasis added)

In first response, Appellant asserts that the Examiner has not persuasively argued that Naggi meets the structural limitations of the invention as claimed, as discussed *supra.*

In second response, Appellant asserts that claim 1 merely claims the existence of an anticoagulant reduction characteristic without placing any limitations on the recited anticoagulant reduction characteristic. Thus, the existence of ***any*** anticoagulant reduction characteristic in Naggi will satisfy the anticoagulant reduction characteristic of claim 1. Appellant asserts that it does not ***necessarily*** follow from the fact that any anticoagulant reduction characteristic in Naggi will satisfy the anticoagulant reduction characteristic of claim 1, that Naggi teaches a super-sulfated oxidized heparin fraction that fully inhibits fibroblast growth factor (FGF2) induced angiogenesis.

In third response, Applicants assert that the allegation in the Examiner's Answer that "there is ***a reasonable expectation*** based on what is disclosed that other characteristics of said

compound are necessarily present" (emphasis added) is an incorrect legal standard for demonstrating inherency. As explained *supra* based on well-established case law, an alleged inherency (that the claimed chemical structure in claim 1 is inherently disclosed by Naggi) must ***necessarily and inevitably*** follow from the teachings in the prior art (i.e., from Naggi) and not from ***reasonable expectation***.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 1 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claim 93

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 93:

"wherein the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof; wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood;

wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a

prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT); and

wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium".

The Examiner argues: "Naggi et al. discloses the reduction of the anticoagulation reduction characteristic with regards to the activated partial thromboplastin time (APTT) (column 9, lines 7-11 and 47-60), explicitly meeting the limitations of instant claims 5 and 93... The depolymerized and supersulfated heparin disclosed by Naggi et al. shows a reduction of the APTT or Anti-Xa as measured in terms of units/mL in table I (column 9, lines 50-65) for products AH-17 and AH-19, relative to the heparin D-212, the reduction being approximately 76.5% (0.05 U/ml / 0.212 U/ml) for the same dose (50 IU/kg), or a reduced prolongation of clotting time of human blood by at least 75% relative to the prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)."

The Examiner's Answer, in "Response to Argument", argues: "Appellant notes that the data in the APTT column of TABLE 1 of Naggi at col. 9, lines 50-59 is not expressed in units of clotting time or prolongation of clotting time, but rather is expressed in units of U/mL. Examiner has cited as evidence definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service to show that determination of levels of anticoagulation are ***known in the art to be acceptably measured in terms of units/mL, or U/mL,*** (Heparin Antifactor Xa Assay, page 2, sections **Reference Interval** and **Use)** ***in addition to units of time.*** The definition of Activated Partial Thromboplastin Time from Massachusetts General Hospital Pathology Service shows the Heparin Antifactor Xa Assay is an equivalent assay to the measurement of Activated Partial Thromboplastin Time (Activated Partial Thromboplastin Time, parage 2, section **Limitations.)** The depolymerized and supersulfated heparin disclosed by Naggi et al. shows a reduction of the APTT or Anti-Xa as measured in terms of units/mL in table I (column 9, lines 50-65) for products AH-17 and AH-19, relative to the heparin D-212, the reduction being approximately 76.5% (0.05 U/ml / 0.212 U/ml) for the same dose (50 IU/kg), or a ***reduced prolongation of clotting time*** of human blood by at least 75% relative to the prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT). The values disclosed by Naggi, expressed in units of U/mL and not units of time, would be understood to be a measure of clotting time or prolongation of clotting time based on the understanding in the art as provided by the evidence of evidence definitions of Activated Partial

Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service."

In response, Appellants assert that the unit of U/ml is a unit of concentration (presumably, a unit of heparin or super-sulfated heparin concentration) and not a unit of time. Claim 93 is claiming activated partial thromboplastin ***time*** (APTT), which is clearly a time and not a concentration. The APTT column of data in Applicant's specification, Par. [0071], Table 2 lists APTT values in units of "seconds" which is a unit of time and not a unit of heparin or super-sulfated heparin concentration.

If the heparin or super-sulfated heparin concentration is indicative of the activated partial thromboplastin time (APTT), it would not matter, because Naggi does not provide a mathematical or graphical relationship between heparin or super-sulfated heparin concentration (as measured in units of U/ml) and activated partial thromboplastin time (APTT) (as measured in units of time). Therefore, there is no way to infer from Naggi what percentage reduction in activated partial thromboplastin time (APTT) corresponds to a 76.5% reduction in super-sulfated heparin concentration for AH-16 or AH-17 in Table I on col. 2, lines 51-59 of Naggi.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 93 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claims 2 and 6

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claims 2 and 6:

"wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic" (claim 2); and

"wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic and the second anticoagulant reduction characteristic" (claim 6).

Claim 93, from which claims 2 and 6 depend, recite:

the first anticoagulant reduction characteristic ("wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood"); and

the second anticoagulant reduction characteristic ("wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)").

The Examiner's Answer, in "Response to Argument", argues: "With regard to claim 2 and 6, the instant specification does not disclose different structural features responsible for claimed properties such as first anticoagulant reduction characteristic and a second anticoagulant reduction characteristic. As recited above with regard to claim 93, the compound disclosed by 10/667,216

Naggi exhibits said second characteristic, therefore there is a ***reasonable expectation*** based on what is disclosed that other characteristics of said compound are necessarily present, see MPEP 2112.01 II, "A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Appellant discloses and/or claims are necessarily present. *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)"." (emphasis added)

In response, Appellants assert that the preceding allegation in the Examiner's Answer that "there is ***a reasonable expectation*** based on what is disclosed that other characteristics of said compound are necessarily present" (emphasis added) is an incorrect legal standard for demonstrating inherency. As explained *supra* in relation to claim 1 based on well-established case law, an alleged inherency must **necessarily and inevitably** follow from the teachings in the prior art (i.e., from Naggi) and not from ***reasonable expectation***.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claims 2 and 6 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claim 5

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 5: "wherein the anticoagulant reduction characteristic comprises the second anticoagulant reduction characteristic ... wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a

condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)".

The Examiner's Answer, in "Response to Argument", argues: "With regard to claim 5, the APTT values disclosed by Naggi, expressed in units of U/mL and not units of time, would be understood to be a measure of clotting time or prolongation of clotting time based on the understanding in the art as provided by the evidence of evidence definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service, as discussed above regarding claim 93".

In response, Appellants assert that the unit of U/ml is a unit of concentration (presumably, a unit of heparin or super-sulfated heparin concentration) and not a unit of time. Claim 5 is claiming activated partial thromboplastin ***time*** (APTT), which is clearly a time and not a concentration. The APTT column of data in Applicant's specification, Par. [0071], Table 2 lists APTT values in units of "seconds" which is a unit of time and not a unit of heparin or super-sulfated heparin concentration.

If the heparin or super-sulfated heparin concentration is indicative of the activated partial thromboplastin time (APTT), it would not matter, because Naggi does not provide a mathematical or graphical relationship between heparin or super-sulfated heparin concentration (as measured in units of U/ml) and activated partial thromboplastin time (APTT) (as measured in units of time). As explained *supra* in relation to claim 93, there is no way to infer from Naggi what percentage reduction in activated partial thromboplastin time (APTT) corresponds to a

76.5% reduction in super-sulfated heparin concentration for AH-16 or AH-17 in Table I on col. 2, lines 51-59 of Naggi.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 5 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claim 91

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 91: "wherein the super-sulfated oxidized heparin fraction comprises a sulfate to carboxylate ratio of about 5:1"

The Examiner's Answer, in "Response to Argument", argues: "With regard to claim 91, Appellants assert that 2.6:1 is not about 5:1, as 5:1 is more than 90% higher than 2.6:1. It is clear that 2.6:1 is not 5:1. However, are recited in the body of the rejection above, "The term "sulfate to carboxylate ratio of about 5:1" in instant claim 91 broadens the ratio without guidance as to the range encompassed by the term "about", and the disclosed sulfation degree of 2.6, or ratio of sulfate to carboxylate of 2.6:1, is interpreted to be about 5:1 because it is the same order of magnitude." Appellants provide no guidance as to metes and bounds of the term "about" in the context of the instant invention, therefore it is maintained that 2.6:1 is **about** 5:1 within the context of the instant invention."

In response, Appellants assert that metes and bounds of the term "about" in the context of an increase from 2.6:1 to 5:1 is not an issue, because the more than 90% change associated with

the increase from 2.6:1 to 5:1 to too large of percent change to permit 2.6:1 to be interpreted as being about 5:1 under any reasonable interpretation of the metes and bounds of the term "about".

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 91 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claim 92

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 92: ", wherein from about 50% to about 100% of primary hydroxyls in ***glucosamine residues*** and secondary hydroxyl groups in ***disaccharide*** units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction".

The Examiner's Answer, in "Response to Argument", argues: "With regard to claim 92, as recited in the body of the rejection above "Naggi et at. discloses a preferred embodiment of depolymerized and supersulfated heparin wherein the molecular weight is 3000-5000 and the sulfation degree is 2.6 (example 12 at column 12, lines 1-30), or a heparin fraction wherein 52% of the primary and secondary hydroxyl groups are substituted by 0-sulfate esters..." This embodiment has 52% hydroxyl groups substituted by 0-sulfate esters, meeting the limitation of instant claim 92."

In response, Appellants assert that the preceding argument in the Examiner's Answer is not persuasive, because the preceding argument in the Examiner's Answer does not address the limitations of the substitutions by 0-sulfate esters occurring at hydroxyl groups in ***glucosamine residues*** and in ***disaccharide*** units.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 92 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claim 94

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 94: "wherein said forming the oxidized heparin fraction comprises O-sulfating the first oxidized heparin fraction by performing sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction"

The Examiner's Answer, in "Response to Argument", argues: "With regard to claim 94, Examiner has cited Naggi at column 4, lines 10-20 and column 5, lines 5-30 to support the chemical reaction implicit in example 12 at column 12, lines 1-30 within Naggi. Therefore Naggi provides evidence that the chemical reaction occurs as described by the Examiner, and the process disclosed by Naggi implicitly anticipates claim 94."

In response, Appellants reiterate, as was stated in the Appeal brief, that the Examiner's description of chemical detail, including intermediate processes, that allegedly occur for EXAMPLE 2 in Naggi, col. 12, lines 1-30 is not disclosed in Naggi. The Examiner has not submitted evidence allegedly demonstrating that the description by the Examiner is correct, especially with regard to intermediate structures produced from treating heparin with sulfuric acid and chlorosulfonic acid.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 94 in "Response to Argument" in the Examiner's Answer are not persuasive.

Claim 43

In the Appeal Brief, Appellant argued that Naggi does not teach the following features of claim 43: "A composition comprising from about 60% to about 100% of the oxidized heparin fraction of claim 1, and from about 0% to about 40% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan sulfates, heparin derivatives, or combinations thereof"

The Examiner's Answer, in "Response to Argument", argues: "With regard to claim 43, the disclosure of Naggi at column 10, lines 55-57 recites the pharmaceutical composition containing the depolymerized and supersulfated heparin of Naggi. As recited in the body of the rejection above, this composition as stated containing said heparin of Naggi is about 100% of said heparin of Naggi. Appellant has not provided evidence that Naggi requires said pharmaceutical composition to contain other than 100% of said heparin of Naggi. Therefore this disclosure by Naggi anticipates claim 43."

In response, Appellants reiterate, as was stated in the Appeal brief, that Naggi, col. 10, lines 55-57 recites "pharmaceutical compositions containing, as active ingredient, a depolymerized and supersulfated heparin of formula IV above" does not teach a "composition comprising from about 60% to about 100% of the oxidized heparin fraction".

The preceding argument in the Examiner's Answer does not even address the recited range of about 60% to about 100% of the oxidized heparin fraction.

Instead, the preceding argument in the Examiner's Answer alleges 100% heparin in the composition, which is outside the recited range of about 0% to about 40% of heparin.

Based on Appellant's preceding analysis, Appellant respectfully contends that the preceding arguments pertaining to claim 43 in "Response to Argument" in the Examiner's Answer are not persuasive.

SUMMARY

In summary, Appellant respectfully requests reversal of the October 27, 2008 Office Action rejection of claims 1, 2, 5-6, 43, 49-54, 56-59, 61-63 and 91-94.

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